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ORIGINAL RESEARCH

Systematic literature review informing the 2022 update of the EULAR recommendations for the management of ANCA-associated vasculitis (AAV): Part 2 - Treatment of eosinophilic granulomatosis with polyangiitis and diagnosis and general management of AAV

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ABSTRACT

Objective To summarise and update evidence to inform the 2022 update of the European Alliance of Associations of Rheumatology (EULAR) recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

Methods Three systematic literature reviews (SLR) were performed. PubMed, EMBASE and the Cochrane library were searched from 1 February 2015 to 25 February 2022. The evidence presented herein covers the treatment of eosinophilic granulomatosis with polyangiitis (EGPA) as well as diagnostic testing and general management of all AAV syndromes.

Results For the treatment of EGPA, diagnostic procedures and general management 3517, 4137 and 4215 articles were screened and 26, 110 and 63 articles were included in the final evidence syntheses, respectively. For EGPA patients with newly diagnosed disease without unfavourable prognostic factors, azathioprine (AZA) combined with glucocorticoids (GC) is not superior to GC monotherapy to induce remission (LoE 2b). In patients with active EGPA and unfavourable prognostic factors, cyclophosphamide or rituximab can be used for remission induction (LoE 2b). Treatment with Mepolizumab added to standard treatment results in higher rates of sustained remission in patients with relapsing or refractory EGPA without active organ-threatening or life-threatening manifestations (LoE 1b) and reduces GC use. Kidney biopsies have prognostic value in AAV patients with renal involvement (LoE 2a). In the context of suspected AAV, immunoassays for proteinase 3 and myeloperoxidase-ANCA have higher diagnostic accuracy compared with indirect immunofluorescent testing (LoE 1a).

Conclusion This SLR provides current evidence to inform the 2022 update of the EULAR recommendations for the management of AAV.

INTRODUCTION

The 2016 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)[1] provided combined treatment recommendations to be applied for eosinophilic granulomatosis with polyangiitis (EGPA) as well as granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), usually based on higher levels of evidence for GPA and MPA, as compared with EGPA. Recent randomised-controlled trials (RCTs) now provide data supporting more specific treatment strategies in EGPA and a separation of the treatment approaches of EGPA and other AAVs.[2–4]

Furthermore, the evidence, on which the recommendations for diagnostic procedures in AAV were made, requires updating in the context of the results of an international collaborative effort of the European Vasculitis Society comparing different methods of ANCA testing,[5] that recently led to an update of the international consensus for testing of ANCA.[6] In more recent EULAR

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Since the publication of the previous European Alliance of Associations of Rheumatology (EULAR) recommendations for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in 2016 several landmark studies improved the treatment concepts in eosinophilic granulomatosis with polyangiitis (EGPA) and led to a new consensus for diagnostic ANCA testing in AAV.

WHAT THIS STUDY ADDS

⇒ Adding azathioprine to glucocorticoids (GC) induction treatment in EGPA without adverse prognostic factors does not improve the rates of initial remission, reduce GC use or prevent disease relapse.

⇒ Cyclophosphamide or rituximab can be used for remission induction in EGPA with adverse prognostic factors.

⇒ Mepolizumab increases the rates of remission and lowers GC need in relapsing or refractory patients with EGPA.

⇒ Conventional immunosuppressives and rituximab may as well improve remission rates and GC demand in patients with refractory or relapsing EGPA.

⇒ Diagnostic accuracy of proteinase 3 and myeloperoxidase-antibody-specific immunoassays is higher compared with ANCA testing by indirect immunofluorescent test.

⇒ Kidney biopsies have predictive value for the development of end-stage kidney disease in AAV.

⇒ Infection prophylaxis with trimethoprim-sulfamethoxazole for AAV patients receiving cyclophosphamide, rituximab and/or high-dose GC may reduce the rates of pneumocystis pneumonia as well as other serious infections.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This systematic literature review will influence the treatment strategies of EGPA and diagnostic strategies in AAV in the following years. It provided the evidence summary for the 2022 Update of the EULAR recommendations for the management of ANCA-associated vasculitis.

recommendations, statements on 'overarching principles' where made that contained aspects of general management of the diseases.[7]

We conducted three systematic literature reviews (SLRs) to inform the 2022 Update of the EULAR recommendations for AAV[8] : on (1) treatment of AAV (of which EGPA is covered in this article), (2) diagnostic testing and follow-up procedures and (3) general management of AAV.

METHODS

The SLRs were performed as outlined in the standard operating procedures for EULAR-endorsed recommendations.[9] A methods protocol was established prior to the conduct of the reviews. The reviews were based on research questions in the patient, intervention, comparator, outcome (PICO) format that were developed before by the task force of the 2022 Update of the EULAR AAV recommendations[8] (including field expert physicians, one healthcare professional and two patient representatives) in a Delphi survey (online supplemental file 1).

Three literature searches were conducted in PubMed, EMBASE and the Cochrane Library databases from 1 February 2015 (since end of the SLR of the last recommendations[1]), until 25 February 2022. The first focused on treatment, the second focused on diagnostic and follow-up procedures and the third focused on aspects of general management. For drug treatments not included in the last recommendations, a search without time restrictions was done. Congress abstracts of the international meetings of EULAR, the American College of Rheumatology, the American Society of Nephrology, the European Renal Association/European Dialysis and Transplant Association and the Vasculitis and ANCA Workshop were also screened for RCTs. Search strings were developed with the assistance of a librarian. Details of the search strategies are presented in the supplementary material (online supplemental file 1). The SLR for treatment was split into two parts: one for treatment of EGPA presented in this article, another for the treatment of GPA and MPA, which is reported separately.

The SLR was performed by two independent reviewers (BS-A and JHS), supervised by two methodologists (GT, RAL). Articles were screened by title and abstract (10% in duplicate with >80% agreement). Both researchers agreed on the included studies. In case of disagreements, consensus was reached by discussion. After selection according to title and abstract screening, articles were evaluated in full text (50% in duplicate). Data elements from articles fulfilling the inclusion criteria were extracted into piloted evidence tables. Data and quality of evidence included in the final SLR report were agreed on by both researchers, in case of disagreements, data were discussed until agreement was reached. Methodologists were consulted in case of uncertainties.

Inclusion criteria were articles in English that provided information with respect to the PICO-questions proposed by the members of the task force (see online supplemental file 1). Case reports, editorials, retrospective studies with mixed populations (not mainly consisting of AAV patients), retrospective studies with <50 patients with GPA/MPA or <20 patients with EGPA and prospective studies with <10 AAV patients as well as diagnostic studies not providing the diagnostic accuracy measures sensitivity, specificity, results from receiver–operator characteristics analyses or predictive value were excluded. For biopsies studies providing diagnostic yield or prognostic value were additionally extracted. For general management, only studies reporting differences of an intervention and a comparator (eg, using vs not using a prophylaxis) or screening procedures and comparators as well as studies reporting harm introduced or prevented by treatments, which were not included in the treatment SLR, were included.

The 2009, Oxford Centre for Evidence-Based Medicine Levels of evidence (LoE) were applied.[10] Risk of bias (RoB) was measured using AMSTAR 2[11] for systematic reviews and meta-analyses, RoB 2 for randomised trials,[12] ROBINS-I for non-randomised intervention studies in the

drug treatment SLR,[13] QUADAS-2 for diagnostic accuracy studies[14] and the Newcastle-Ottawa-Scale for case series, self-controlled before–after studies, cohort studies reporting multiple factors associated with outcomes of interest and other studies.[15]

RESULTS

The three literature searches focusing on EGPA treatment, diagnosis and follow-up testing and general management identified 3517, 4137 and 4215 articles, respectively (after deduplication). After title/abstract screening, 175, 205 and 177 articles were selected for full-text review (online supplemental file 1). Twenty six articles[2–4 16–38] on treatment of EGPA (online supplemental file 2), 110 articles[5 39–147] on diagnostic procedures and follow-up testing (online supplemental file 3) and 63 articles[106 126 148–208] on general management (online supplemental file 3) were ultimately included.

Section A: treatment of EGPA

According to the common conceptual framework regarding treatment of AAV, we report separately on treatment for remission induction and remission maintenance. However, some of the trials included provide evidence towards both of these broad categories of disease management, that is both remission induction as well as relapse prevention and glucocorticoids (GC)-sparing effects.[2 3 25]

Remission induction treatment

Glucocorticoid monotherapy and conventional immunosuppressives

The randomised CHUSPAN2 trial (table 1) included 95 patients with newly diagnosed necrotising vasculitis (51 with EGPA, 25 with MPA and 19 with polyarteritis nodosa) without negative prognostic factors (defined by the 1996 five-factor score (FFS) of 0).[3 25] It compared azathioprine (AZA) versus placebo in addition to glucocorticoid (GC) treatment (starting with 1 mg/kg/day for 3 weeks, then consecutively tapered over approximately 48 to 52 weeks until discontinuation or in EGPA reaching of the lowest dose needed for control of asthma symptoms). The primary outcome (combined rate of remission induction failures and relapses at month 24) was not different between the trial arms (neither for the whole trial population, nor for the EGPA subgroup, table 1). Initial remission rates were also not different in patients treated with GC and AZA compared with GC and placebo in the overall trial population. In the EGPA subpopulation, there were no initial remission failures in the group treated with GC and AZA. In the GC plus placebo group, one death after remission failure was observed.

For relapsing or refractory cases of EGPA, retrospective case-series suggest that conventional immunosuppressives (MTX, AZA or leflunomide) may increase remission rates and reduce GC dependency.[19] These findings are consistent with RCTs that precede the period that is the focus of this literature review and are briefly summarised to provide context (these studies were included in previous EULAR recommendations and a recent SLR)[1 27 209]: In an RCT published by *Ribi et al*, 72 newly diagnosed EGPA patients with a FFS of 0 were initially treated with a GC monotherapy induction (without control group).[210] Ninety-three per cent reached initial remission, 7% did not and 27 of 67 (40%) patients with initial remission relapsed (37%) or had GC-dependent disease (3%). Nineteen patients who did not achieve remission, relapsed or were GC dependent were then randomised to receive either cyclophosphamide (CYC) (n=10) or AZA (n=9). Remission rates achieved after CYC and AZA treatment were not different, but the trial may be underpowered due to low patient numbers in the randomised arms. Adverse events included infections requiring hospitalisation in 8 of 72 (11%) and osteoporotic fractures in 7 of 72 (10%) of patients. *Metzler et al* reported successful remission induction treatment using MTX and GC in 8 of 11 patients with EGPA in an open-label trial.[211]

Available studies on GC monotherapy and treatment with conventional immunosuppressives may be driven by bias to some extent as the subjects of the trials include patients with a mixture of different AAVs and the initially high GC doses that could mask the efficacy of cotreatments. Furthermore, a previously published subanalysis of two RCTs has reported that mononeuritis multiplex (a factor not included in the FFS) also shows the need for additional immunosuppressive treatment.[212]

In summary, GC monotherapy for newly diagnosed EGPA carries a high risk of both disease relapse and GC-associated adverse events (LoE 4). However, for patients without unfavourable prognostic factors, the addition of AZA to GC for remission induction does not provide benefit with respect to initial remission rates, GC-sparing or relapse rates (LoE 2b). Evidence on the use of other conventional immunosuppressives in EGPA without unfavourable prognostic factors to achieve remission and lower GC doses is low (LoE 4).

Cyclophosphamide and rituximab

The recent RCTs for remission induction in EGPA build on evidence for the effectiveness of CYC. A trial by Cohen *et al* that was published before the period covered by this SLR, randomised 48 patients with recently diagnosed EGPA and FFS ≥1 to receive either 6 or 12 pulses of CYC and GC.[27 213] 91.3% in the 6-pulse arm and 84% in the 12 pulse arm reached complete remission. The overall rate of relapses (6 pulses: 78% vs 12 pulses: 52%) was not significantly different, but minor relapse rate was lower in the 12 pulse arm (6 pulses: 77.7% vs 12 pulses: 46.1%, p=0.02).

The REOVAS trial compared a rituximab (RTX) based regimen to conventional regimens for remission induction in EGPA.[4] It included 105 patients with newly diagnosed or relapsing EGPA and compared RTX or RTX-placebo added to standard induction treatment. Patients with a FFS=0 were randomised to GC+RTX vs GC+placebo. Patients with FFS >0 were randomised to

Table 1 Randomised controlled trials in EGPA

Methotrexate

Study ID	Included patients	n	Intervention	Control	Primary endpoint	Result intervention	Result control	Significance	Comment
Maritati *et al*[37] 2017 PLOS One (POWERCIME)	GPA, MPA, EGPA, newly diagnosed or relapsing / refractory	30 EGPA	MTX (+ GC) after induction with CYC	CYC (+ GC) after induction with CYC	Relapse frequency by month 12.	1 of 17 (6%)	1 of 13 (8%)	p=1.00, relapse-free survival log-rank: p=0.78	Subgroup results for EGPA

Azathioprine

Study ID	Included patients	n	Intervention	Control	Primary endpoint	Result intervention	Result control	Significance	Comment
Puéchal *et al*. A&R 2017 (CHUSPAN2)[3] [25]	MPA, EGPA, PAN, newly diagnosed, FFS=0	All patients: 101 allocated, 95 received intervention	AZA (+ GC)	Placebo (+ GC)	Combined rate of remission induction failure or relapse at month 24	All patients: 22 of 45 (47.8%)	All patients: 24 of 49 (49%)	All patients: OR 1.08 (95% CI 0.46 to 2.52); p=0.86	
		EGPA: 51				EGPA: 12 of 25 (48%)	EGPA: 12 of 26 (46.2%)	EGPA: OR 1.09 (95% CI 0.33 to 3.65)	Subgroup results for EGPA

Rituximab

Study ID	Included patients	n	Intervention	Control	Primary endpoint	Result intervention	Result control	Significance	Comment
Terrier *et al*. A&R 2021 (REOVAS)[4]	EGPA, relapsing or newly diagnosed	105	RTX (+ placebo CYC if FFS≥1) + GC	Placebo RTX (+ CYC if FFS≥1) + GC	Remission at day 180	33 of 52 (63.5%)	32 of 53 (60.4%)	RR 1.05 (95% CI 0.78 to 1.42); p=0.75	Abstract

Mepolizumab

Study ID	Included patients	n	Intervention	Control	Primary endpoint	Result intervention	Result control	Significance	Comment
Wechsler et al. NEJM 2017 (MIRRA)[2]	EGPA, relapsing or refractory	136	MEPO (+ GC ± immunosuppressive)	Placebo (+ GC ± immunosuppressive)	1. Total accrued weeks of remission 2. Proportion of participants with remission at week 36 and 48	1. 19 of 68 (28%) ≥ 24 weeks 2.22 of 68 (32%)	1. 2 of 68 (3%) ≥ 24 weeks 2.2 of 68 (3%)	1. OR 5.91 (95% CI 2.68 to 13.03); p<0.001 2. OR 16.74 (95% CI 3.61 to 77.56); p<0.001	

Reduced doses of Glucocorticoids and Cyclophosphamide in patients≥65 years

Study ID	Included patients	n	Intervention	Control	Primary endpoint	Result intervention	Result control	Significance	Comment
Pagnoux *et al*. A&R 2015 (CORTAGE)[38]	GPA, MPA, EGPA, PAN, age≥65 years, newly diagnosed	14 EGPA	GC discontinued at 9 months, max. 6x pulse CYC 500 mg until remission, maintenance with MTX/ AZA/MMF	GC discontinued at 26 months, 6x pulse CYC 500 mg/m^2, maintenance with MTX/ AZA/MMF. Patients with EGPA or PAN and FFS=0 received only GC.	≥1 SAE	6 of 8 (75%)	4 of 6 (67%)	NA	Subgroup results for EGPA

AZA, azathioprine; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; FFS, five-factor score; GC, glucocorticoids; GPA, granulomatosis with polyangiitis; MEPO, mepolizumab; MMF, mycophenolate mofetil; MPA, microscopic polyangiitis; MTX, methotrexate; PAN, polyarteritis nodosa; RTX, rituximab.

receive GC+RTX vs GC+CYC. The remission rate achieved at day 180 was not significantly different between groups (table 1). Availability of details of the REOVAS trial was limited because the data were only published as congress abstract at the time of the SLR. In a retrospective cohort study by *Thiel et al,* RTX was used for induction treatment in 14 patients with relapsing or refractory EGPA and compared with matched controls receiving CYC.[29] Similar response rates were seen in both groups. Other studies reporting the use of RTX (without control group) also report response or remission of EGPA after treatment with RTX.[18 28]

The updated SLR further identified two RCTs in which CYC induction was used to treat EGPA patients.[37 38] The conclusions for induction treatment of EGPA that can be drawn from them are limited: both trials included patients with different vasculitis diagnoses. *Maritati et al* focused on maintenance treatment and did not report a result of the efficacy of CYC for remission induction in EGPA,[37] the CORTAGE trial included only a low number of EGPA patients.[38]

In summary, moderate to high-quality evidence suggests similar efficacy of either CYC or RTX, in combination with high-dose GC, for remission induction in EGPA for patients with unfavourable prognostic factors (LoE 2b).

Mepolizumab

The randomised MIRRA trial compared the interleukin 5—inhibitor mepolizumab (MEPO) or placebo added to standard treatment (consisting of GCs with or without immunosuppressives as AZA, MTX or MMF) over 52 weeks.[2] It included patients with EGPA that had either relapsing or refractory disease course. Patients with active organ-threatening or life-threatening disease were excluded. The trial met its both primary efficacy endpoints (table 1): the first, accrued weeks in remission (defined as BVAS of 0 and a prednisolone dose ≤4 mg/day): 28% in the MEPO group versus 3% in the placebo group had ≥24 weeks of accrued remission. The second primary endpoint was the percentage of patients in remission at both, weeks 36 and 48, which was achieved in 32% in the MEPO group and 3% in the placebo group. 47% in the MEPO arm and 81% in the placebo arm did not achieve remission.

In summary, MEPO added to standard treatment consisting of GC with or without conventional immunosuppressives for induction shows higher rates of sustained remission and GC sparing properties in patients with relapsing or refractory EGPA without active organ-threatening or life-threatening manifestations (LoE 1b).

Remission maintenance

Only one new RCT was identified, which investigated remission maintenance treatment in EGPA. The POWERCIME trial compared remission maintenance treatment with CYC vs MTX added to GC after reaching remission under CYC induction.[37] The trial enrolled a mixed AAV population, 30 of the 71 included patients had EGPA (with either unfavourable prognostic factors defined by a FFS≥1 or peripheral neuropathy), a subgroup analysis showed no significant difference in relapse-free survival among patients with EGPA but is likely underpowered to detect differences due to low EGPA subgroup numbers (table 1). In recent studies including EGPA with unfavourable prognostic factors, maintenance with a conventional immunosuppressive was usually prescribed after induction treatment[4 38] but apart from the EGPA subgroup of the POWERCIME trial[37] and retrospective reports of GC-sparing properties of conventional immunosuppressives in relapsing and refractory EGPA,[19] there is little evidence for the efficacy of these agents for remission maintenance. In a trial preceding the period covered by this SLR, *Metzler et al* reported relapses in 12 of 23 EGPA patients with long-term follow-up data receiving MTX for remission maintenance.[211]

The MIRRA and CHUSPAN2 trials, included patients with active EGPA who received placebo or active treatment (MEPO in MIRRA, AZA in CHUSPAN2) added to conventional therapy. Although the focus of these RCTs is induction treatment, their long follow-up periods provide information on relapse prevention and glucocorticoid sparing. Patients who received MEPO accrued more weeks in remission and received less GC compared with placebo (table 1). A relapse occurred in 56% of patients treated with MEPO compared with 82% treated with standard treatment (annualised relapse rate 1.14 for MEPO arm and 2.27 in placebo arm; rate ratio 0.50, 95% CI 0.36 to 0.70; p<0.001). Average GC doses during weeks 48 to 52 were lower in participants in the MEPO-arm compared with the placebo arm (44% in the MEPO group vs 7% in the placebo group took 4 mg prednisone or less daily during this period, OR 0.20, 95% CI 0.09 to 0.41, p<0.001). Eighteen per cent receiving MEPO versus 3% in the placebo arm were able to discontinue GC.[2]

The CHUSPAN2 trial did not find that AZA reduced GC use or relapse rate for EGPA patients (p=0.34) (nor was such effect found in the trial at large which included subjects with other types of vasculitides).

A small case-series described low rates of disease relapse in EGPA with scheduled RTX retreatment at a dose of 500 mg every 6 months (LoE 4).[33]

In summary, there is scant evidence from RCTs to guide maintenance treatment in EGPA. Efficacy of MTX is comparable to CYC for remission maintenance in EGPA with unfavourable prognostic factors (LoE 2b). MEPO is effective for prevention of relapses and as a GC-sparing agent in refractory or relapsing EGPA (LoE 1b). For EGPA in patients without unfavourable prognostic factors, addition of AZA to GC induction does neither prevent relapses nor reduce GC use (LoE 2b). Evidence for other conventional immunosuppressives or RTX is scarce.

Glucocorticoid dosing

Studies specifically comparing different GC tapering schedules in EGPA were not identified (except for the CORTAGE

trial which included only 14 EGPA patients).[38] In a retrospective study of EGPA patients, the duration of GC treatment was associated with higher vasculitis damage index (increased by 0.5% for each additional month of GC treatment, the result remained significant in the multivariate analysis adjusted for follow-up duration).[32]

Section B: Diagnostic and follow-up procedures for AAV

Biopsies for diagnosis of AAV

No new studies that reported diagnostic accuracy measures (eg, sensitivity, specificity) of biopsies in AAV were identified. Different diagnostic yields of biopsies were reported, depending on clinical constellations and organs biopsied. Diagnostic yield was reported to be up to 50% in nasal or paranasal sinus biopsies (GPA),[103 118] up to 53% in nerve biopsies performed in AAV patients with vasculitic neuropathy,[46 114] up to 60% in muscle biopsies[63 97] and 92% in kidney biopsies of patients with renal involvement and an active urine sediment with major changes.[83] A retrospective study, that included low numbers of pulmonary biopsies, reported diagnostic yield for GPA to be low when using fine needle biopsies (n=8 with 100% unspecific findings) but high diagnostic yield for bronchus biopsies (n=3 with 67% showing typical findings for GPA) and open lung or punch-biopsies (n=5, 80% typical findings for GPA).[103]

No imaging studies were identified, which provide diagnostic features specific enough to replace diagnostic biopsies (even though imaging is often used to detect certain manifestations of AAV).

In summary, no new evidence for the diagnostic accuracy of biopsies was identified. Negative biopsies do not rule out AAV.

Tissue biopsies for assessing disease prognosis in AAV

Several scoring systems for renal biopsies have demonstrated their prognostic value for the recovery of renal function or progression of ESKD. The classification proposed by an international working group in 2010 (Berden *et al*)[214] divides glomerular pathology in AAV into four histopathology classes (*focal*, *crescentic*, *mixed* and *sclerotic*) and has been evaluated in a number of studies.[41–43 48 49 52 60 61 64 66 70 74 77–79 89 95 102 111 122 131 136 139] Meta-analyses demonstrate that the *focal* subclass is associated with better renal survival, whereas the *sclerotic* class is associated with worse renal survival compared with the other classes (table 2). *R*isk of ESKD was not demonstrated to be significantly lower in *focal* class compared with *mixed* class.[89] Meta-analyses have not demonstrated different risk of ESKD between the *mixed* and *crescentic* classes. A recently published renal risk score divides patients into a low, medium and high risk for ESKD based on the percentage of normal glomeruli, interstitial fibrosis and tubular atrophy as well as estimated glomerular filtration rate (eGFR) at diagnosis[54] and has been evaluated by numerous studies.[41 43 52 74 77 78 99 107 128 131 136 143] Pooled estimates of ESKD rates of patients in the low-risk, medium-risk and high-risk group from a recent meta-analysis[138] are shown in table 2. The Mayo Clinic Chronicity score[215] has also been shown to have prognostic value for ESKD in AAV.[41 45 112]

In summary, substantial evidence supports that kidney biopsies have prognostic value in AAV patients with renal involvement (LoE 2a).

ANCA testing for diagnosis of AAV

Comparative multicentre studies recently described diagnostic accuracy to be higher in antigen-specific immunoassays for proteinase 3 (PR3) and myeloperoxidase (MPO) compared with the indirect immunofluorescent testing (IIF, table 3) for ANCA in GPA and MPA.[5 67 145] The diagnostic accuracy of different IIF methods varies.[5 67] A recent meta-analysis including 13 diagnostic studies (some of them including EGPA patients) supports these results (table 3).[81] No studies reporting sensitivity and specificity solely for EGPA were identified.

In summary, in the context of suspected AAV, antigen-specific assays for PR3 and MPO can be used as first-line serologic diagnostic tests without need for previous IIF (LoE 1a).

Follow-up monitoring

Several studies report persistently positive ANCA levels during remission, switch from negative to positive ANCA or rising ANCA titres to be significantly associated with relapses, persistently negative ANCA on the other hand are associated with sustained remission.[40 62 76 84 92 104–106 110 116 121 130 132 137 140] Undetectable B cells after RTX treatment are associated with low relapse risk and most relapsing patients have recovery of B cells.[92 104 129 132] However, rise of ANCA titres and B cell recovery are not followed by relapses in a substantial proportion of patients and relapses are also reported in patients with negative ANCA (or no rise in titre) and/or with persistently negative B cells after RTX treatment.[59 76 104 119 132 137] Persistent (micro)haematuria is associated with increased risk of relapse and reduction in glomerular filtration rate.[58 62 101 120 133] Inflammatory parameters available in routine clinical care (C reactive protein, erythrocyte sedimentation rate) as well as eosinophil counts (in EGPA) seem to correlate with disease activity in AAV to some extent. Procalcitonin might have some value to discriminate active vasculitis and infections, but high-quality studies are lacking.[80 85 96]

In summary, disease activity state and need for changes in treatment cannot be derived from ANCA titres or B cell counts alone (LoE 1b). There remains an unmet need for sensitive and specific parameters for disease monitoring in AAV.

Section C: general management

Risk factors for infectious complications and infection prophylaxis

Some recent studies report infections to be associated with CYC exposure,[126 164 172 174 208] pulse GC treatment (or high doses of GC)[126 153 155 164 192 207] and hypogammaglobulinaemia.[106] However, other studies have not found CYC[153 155 165 177] and GC exposure (or pulses)[165 172 174 177 188] to be associated with risk of infection.

Table 2 Meta-analyses of studies evaluating prognostic accuracy of scoring systems for kidney biopsies in AAV

Berden classification									
Study ID	**Prognostic class**	**Control**	**Outcome**	**Included studies**	**Number of participants**	**Summary estimate**	**Effect size**	**Heterogeneity**	**Comment**
Chen *et al*. J Rheumatol. 2017 [61]	Focal	Crescentic	ESKD	16	884	RR (95% CI)	0.23 (0.16 to 0.34)	I^2=0%	
Huang *et al*. International Urology and Nephrology 2018 [89]	Focal	Crescentic	Renal survival	9	775	HR (95% CI)	0.46 (0.27 to 0.78)	I^2=0%	Bayesian Network Meta-Analysis: HR 0.54 (95% CI 0.35 to 0.86)
Huang *et al*. International Urology and Nephrology 2018 [89]	Focal	Mixed	Renal survival	8	595	HR (95% CI)	0.58 (0.32 to 1.07)	I^2=5%	Bayesian Network Meta-Analysis: HR 0.73 (95% CI 0.41 to 1.32)
Huang *et al*. International Urology and Nephrology 2018 [89]	Focal	Sclerotic	Renal survival	9	470	HR (95% CI)	0.20 (0.12 to 0.33)	I^2=0%	Bayesian Network Meta-Analysis: HR 0.24 (95% CI 0.12 to 0.51)
Chen *et al*. J Rheumatol. 2017 [61]	Crescentic	Mixed	ESKD	16	878	RR (95% CI)	1.14 (0.91 to 1.43)	I^2=23%	
van Daalen *et al*. Clinical Journal of the American Society of Nephrology 2020 [131]	Crescentic	Mixed	Kidney failure	21	1526	RR (95% CI)	1.15 (0.94 to 1.41)	I^2=23%	
Huang et al. International Urology and Nephrology 2018 [89]	Crescentic	Mixed	Renal survival	12	928	HR (95% CI)	1.25 (0.83 to 1.88)	I^2=19%	Bayesian Network Meta-Analysis: HR 1.35 (95% CI 0.90 to 2.0)
Chen *et al*. J Rheumatol. 2017 [61]	Crescentic	Sclerotic	ESKD	16	613	RR (95% CI)	0.52 (0.41 to 0.64)	I^2=2%	
Huang *et al*. International Urology and Nephrology 2018 [89]	Crescentic	Sclerotic	Renal survival	11	689	HR (95% CI)	0.47 (0.31 to 0.71)	I^2=19%	Bayesian Network Meta-Analysis: HR 0.45 (95% CI 0.26 to 0.79)
Chen *et al*. J Rheumatol. 2017 [61]	Mixed	Sclerotic	ESKD	16	595	RR (95% CI)	0.42 (0.33 to 0.54)	I^2=33%	
Huang *et al*. International Urology and Nephrology 2018 [89]	Mixed	Sclerotic	Renal survival	10	625	HR (95% CI)	0.33 (0.23 to 0.47)	I^2=0%	Bayesian Network Meta-Analysis: HR 0.34 (0.22 to 0.51)
Renal risk score									
Study ID	**Prognostic class**	**Control**	**Outcome**	**Included studies**	**Number of participants**	**Summary estimate**	**Effect size**	**Heterogeneity**	**Comment**
Xia *et al*. *Frontiers in Medicine* [138]	RRS 0 to 1	–	Cumulative ESKD	7	309	Effect (95% CI)	0.05 (0.02 to 0.07)	I^2=0%	
	RRS 2 to 7	–	Cumulative ESKD	12	726	Effect (95% CI)	0.22 (0.15 to 0.29)	I^2=86%	
	RRS 8 to 11	–	Cumulative ESKD	12	434	Effect (95% CI)	0.59 (0.49 to 0.69)	I^2=77%	

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; ESKD, end-stage kidney disease.

Table 3 Diagnostic accuracy studies for ANCA testing

Meta-analyses

Study ID	Test	Reference	Included studies	Number of subjects	Pooled sensitivity (95% CI)	Pooled Specificity (95% CI)	LR+	LR–	Comment
Guchelaar *et al*. Autoimmunity Reviews 2021[81]	C-ANCA (IIF)	Diagnosis of AAV	9	9682	75.2% (60.7% to 85.6%)	98.4% (92.8% to 99.7%)	47	0.25	
	P-ANCA (IIF)	Diagnosis of AAV	4	7313	46.3% (14.4% to 81.6%)	91.4% (80.8% to 96.4%)	5.38	0.59	
	PR3 (direct immunoassay)	Diagnosis of AAV	10	10088	79.8% (59.0% to 91.9%)	98.3% (93.9% to 99.5%)	47	0.21	
	PR3 (capture immunoassay)	Diagnosis of AAV	4	1299	84.9% (71.0% to 92.8%)	98.8% (97.2% to 99.5%)	71	0.15	
	PR3 (anchor immunoassay)	Diagnosis of AAV	5	2537	86.6% (74.8% to 93.3%)	96.8% (91.8% to 98.8%)	27	0.14	
	MPO (immunoassay)	Diagnosis of AAV	5	7486	58.1% (34.6% to 78.5%)	95.6% (92.0% to 97.6%)	13	0.44	

Validating cohort studies

Study ID	Test	Reference	Number of subjects	Number of tests	Sensitivity GPA	Sensitivity MPA	Sensitivity AAV	Specificity	LR+ (AAV)	LR– (AAV)	AUC AAV (95% CI)	Comment
Csernok *et al*. Autoimmunity Reviews 2016[67]	ANCA IIF (manual)	Diagnosis of AAV/GPA/MPA	183 GPA 66 MPA 912 Controls	2	80.3% and 88.5%	90.9% and 93.9%	83.9% and 89.2%	78.6% and 94.0%	3.9 and 14.8	0.12 and 0.20	0.848 (0.821 to 0.876) and 0.925 (0.904 to 0.946)	
	ANCA IIF (automated)	Diagnosis of AAV/GPA/MPA	183 GPA 66 MPA 912 Controls	2	66.1% and 89.6%	86.4% and 87.9%	71.5% and 89.2%	89.4% and 89.8%	6.7 and 8.7	0.12 to 0.32	0.855 (0.828 to 0.882) and 0.904 (0.882 to 0.927)	
	MPO/PR3 (automated)	Diagnosis of AAV/GPA/MPA	183 GPA 66 MPA 912 Controls	2	85.2% and 88.0%	75.8% and 77.3%	83.1% and 84.7%	94.1% and 94.6%	14.0 and 15.8	0.16 to 0.18	0.886 (0.862 to 0.911) and 0.921 (0.894 to 0.947)	
	MPO/PR3 (ELISA)	Diagnosis of AAV/GPA/MPA	183 GPA 66 MPA 912 Controls	1	89.6%	90.9%	90.0%	96.8%	28.3	0.10	0.959 (0.942 to 0.977)	AUC in ELISA significantly higher compared with all IIF methods ($p<0.0001$).

Continued

Table 3 Continued

Validating cohort studies												
Damoiseaux *et al*. Annals of the Rheumatic Diseases 2017 [5]	C-ANCA (IIF)	Diagnosis of AAV/GPA/MPA	186 GPA 65 MPA 924 Controls	2	64% and 78%.	5% and 6%	–	97% and 98%	–	–	0.842 (0.814 to 0.871) and 0.923 (0.902 to 0.944)	
	P-ANCA (IIF)	Diagnosis of AAV/GPA/MPA	186 GPA 65 MPA 924 Controls	2	11% and 14%	85% and 89 %	–	81% and 96%	–	–		
	PR3 (immunoassay)	Diagnosis of AAV/GPA/MPA	186 GPA 65 MPA 924 Controls	8	75% to 80%	3% to 6%	–	98% to 99%	–	–	0.919 (0.892 to 0.945) to 0.959 (0.941 to 0.976)	AUC of all immunoassays significantly higher compared with first IIF and AUC of all but one immunoassay significantly higher compared with second
	MPO (immunoassay)	Diagnosis of AAV/GPA/MPA	186 GPA 65 MPA 924 Controls	8	3% to 6%	68% to 86%.	–	96% to 99%	–	–		
Kempiners *et al*. Rheumatology 2021 [93]	ANCA (IIF)	Diagnosis of AAV	34 GPA 16 MPA 45 Controls	1	–	–	84%	91.1%	9.44	0.18	0.858 (0.785 to 0.931)	
	PR3/MPO (immunoassays)	Diagnosis of AAV	34 GPA 16 MPA 45 Controls	5	–	–	74% to 96%	82.2% to 95.6%	5.39 to 16.82	0.05 to 0.27	0.869 (0.797 to 0.941) to 0.936 (0.886 to 0.985)	AUCs between tests comparable but one LIA outperformed IIF
Zhang *et al*. Clinical Rheumatology 2019 [145]	ANCA (IIF)	Diagnosis of AAV/GPA/MPA	153 MPA 56 GPA 243 Controls	2	58.9% and 71.4%	79.1% and 82.4%	76.1% and 77.0%	89.7% and 97.1%	7.48 and 26.24	0.25 and 0.26	0.886 (0.826 to 0.946) to 0.891 (0.831 to 0.951)	
	PR3/MPO (immunoassays)	Diagnosis of AAV/GPA/MPA	153 MPA 56 GPA 243 Controls	10	82.1% to 96.1%	65.4% to 98.0%	71.8% to 96.7%	96.3% to 99.2%	23.2 to 90.87	0.03 to 0.28	0.846 (95% CI 0.779 to 0.913) to 0.981 (95% CI 0.959 to 1)	AUC of all quantitative immunoassays higher compared with IIF ($p<0.01$)

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AUC, area under the curve; GPA, granulomatosis with polyangiitis; IIF, indirect immunofluorescent testing; LR+, positive likelihood ratio: sensitivity / (1 - specificity); LR-, negative likelihood-ratio (1 - sensitivity) / specificity; MPA, microscopic polyangiitis; MPO, myeloperoxidase.

Table 4 Main conclusions

Main conclusions		
Area	**Subcategory**	**Conclusion**
EGPA remission induction	GC monotherapy, AZA, other conventional immunosuppressives	GC monotherapy for newly-diagnosed EGPA carries a high risk of both disease relapse and GC-associated adverse events (LoE 4). However, for patients without unfavourable prognostic factors, the addition of AZA to GC for remission induction does not provide benefit with respect to initial remission rates, GC-sparing or relapse rates (LoE 2b). Evidence on the use of other conventional immunosuppressives in EGPA without unfavourable prognostic factors to achieve remission and lower GC doses is low (LoE 4).
EGPA remission induction	CYC, RTX	Moderate to high-quality evidence suggests similar efficacy of either CYC or RTX, in combination with high dose GC, for remission induction in EGPA patients with unfavourable prognostic factors (LoE 2b).
EGPA remission induction	MEPO	MEPO added to standard treatment consisting of GC with or without conventional immunosuppressives for induction shows higher rates of sustained remission and GC sparing properties in patients with relapsing or refractory EGPA without active organ- or life-threatening manifestations (LoE 1b).
EGPA remission maintenance	GC, CYC, MTX, MEPO, AZA, RTX, other conventional immunosuppressives	There is scant evidence from RCTs to guide maintenance treatment in EGPA. Efficacy of MTX is comparable to CYC for remission maintenance in EGPA with unfavourable prognostic factors (LoE 2b). MEPO is effective for prevention of relapses and as a GC-sparing agent in refractory or relapsing EGPA (LoE 1b). For EGPA in patients without unfavourable prognostic factors, addition of AZA to GC induction does neither prevent relapses nor reduce GC use (LoE 2b). Evidence for other conventional immunosuppressives or RTX is scarce.
Biopsies	Diagnostic accuracy	No new evidence for the diagnostic accuracy of biopsies was identified. Negative biopsies do not rule out AAV.
Biopsies	Prognosis	Substantial evidence supports that kidney biopsies have prognostic value in AAV patients with renal involvement (LoE 2a).
Diagnostic biomarkers	ANCA (IIF, MPO, PR3)	In the context of suspected AAV, antigen-specific assays for PR3 and MPO can be used as first-line serologic diagnostic tests without need for previous IIF (LoE 1a).
Follow-up testing	ANCA (IIF, MPO, PR3), B cell counts	Disease activity state and need for changes in treatment cannot be derived from ANCA titres or B cell counts alone (LoE 1b). There remains an unmet need for sensitive and specific parameters for disease monitoring in AAV.
General management	Infection prophylaxis	TMS prophylaxis may reduce the risk of pneumocystis pneumonia and other severe infections in patients treated with CYC, RTX or high-dose GC (LoE 3b).
General management	Malignancy risk	CYC exposure is a risk factor for malignancy in AAV (LoE 2b).

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoids; IIF, indirect immunofluorescent testing; LoE, level of evidence; MEPO, mepolizumab; MPO, myeloperoxidase; MTX, methotrexate; PR3, proteinase 3; RCT, randomised-controlled trial; RTX, rituximab; TMS, trimethoprim-sulfamethoxazole.

Infection prophylaxis with trimethoptim/sulfamethoxazole (TMS) reduces severe infections AAV (mostly treated with CYC or RTX).[162 171 176 201] TMS also reduced the incidence of pneumocystis jirovecii pneumonia in a cohort study of patients with various rheumatic diseases (including AAV) receiving ≥30 mg prednisone equivalent for ≥4 weeks[185] and in a retrospective cohort study of >20 000 patients with rheumatic diseases, including 430 patients with AAV.[157]

Park et al estimated that the number needed to treat to prevent one case of pneumocystis infection (52, 33 to 124) was lower than the number needed to harm for serious drug reactions (131, 55 to ∞).[185]

In patients with rheumatic diseases treated with GC doses <30 mg prednisone (or equivalent) pneumocystis infections are rare and mainly occur in the presence of additional risk factors (eg, GC pulses, CYC treatment or lymphopenia). A statistically significant effect of TMS prophylaxis could not be demonstrated in this subgroup.[184]

In summary, TMS prophylaxis may reduce the risk of pneumocystis pneumonia and other severe infections in patients treated with CYC, RTX or high-dose GC (LoE 3b).

Risk of malignancy

The risk of cancer has been reported to be higher in patients with AAV patients compared with general population.[148] There is consistent data showing an increased incidence of non-melanoma skin cancer among patients with AAV.[167 187 216] Some reports suggest an increased risk for bladder cancer and myeloid leukaemia, especially among patients exposed to high cumulative CYC doses.[160 216] CYC exposure is a risk factor for malignancy in AAV in a dose-dependent way,[148 158 160 167 187 200] whereas one study found no association between rituximab exposure and malignancy in AAV.[200] No new studies reporting the efficacy of targeted malignancy screening strategies were identified.

Table 5 Research agenda/unmet needs

Research agenda		
Area	**Subcategory**	**Research topics**
EGPA remission induction	GC monotherapy, conventional immunosuppressives, CYC, RTX, anti-IL5 therapy	► Efficacy and safety of MEPO for EGPA with organ-threatening disease (compared with CYC and RTX) or newly-diagnosed EGPA without unfavourable prognostic factors ► Efficacy and safety of IL5-targeting medications other than MEPO for EGPA ► Value of conventional immunosuppressives and RTX as GC-sparing substances added to GC for EGPA without unfavourable prognostic factors
EGPA remission maintenance	GC, CYC, MTX, anti-IL5-therapy, AZA, RTX, other conventional immunosuppressives	► Efficacy and safety of MEPO, other IL5-targeting medications, RTX and other conventional immunosuppressives for GC sparing and remission maintenance in EGPA ► Evidence-based management of sinonasal disease and asthma to reduce GC dependency
Glucocorticoids*	GC	► Data-driven recommendations for the use of GC pulses and optimal GC dosing and tapering with respect to infection and relapse risk
Diagnosis*	Data-driven criteria and definitions	► Data-driven diagnostic criteria ► Data-driven disease activity states and standardised outcome measures
Prognosis, personalised treatment*	Biomarkers, clinical criteria	► Biomarker and phenotype driven personalised treatment strategies ► Data-driven criteria for the need of additional treatment (to be comined with GC) in EGPA ► Data-driven treatment recommendations incorporating prognostic value of biopsies
Follow-up testing*	Biomarkers	► Biomarkers for disease activity monitoring and prediction of relapse
General Management*	Infection prophylaxis	► Required dosage and duration of TMS prophylaxis. ► Data-driven criteria for immunoglobulin supplementation in case of hypogammaglobulinaemia. ► Optimised use of vaccinations.
General management*	Quality of life, patient-reported outcomes, fatigue	► Data-driven treatment and management strategies to improve patient-reported outcomes including fatigue and providing psychological and occupational support
General management	Other	► Optimised treatment schedules for elderly AAV patients ► Evidence-based strategies for prevention of comorbidities (eg, malignancies, cardiovascular and thrombembolic adverse events) ► Evidence-based strategies for contraception, pregnancy and family planning ► Evidence-based lifestyle inteventions for improving prognosis in AAV

*, Several aspects also apply to Granulomatosis with polyangiitis and Microscopic polyangiitis; AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; CYC, cyclophosphamide; EGPA, eosinophilic granulomatosis with polyangiitis; GC, glucocorticoids; MEPO, mepolizumab; MTX, methotrexate; RTX, rituximab; TMS, trimethoprim-sulfamethoxazole.

In summary, CYC exposure is a risk factor for malignancy in AAV (LoE 2b).

Other aspects of management of AAV

Limited AAV-specific data are available for factors associated with cardiovascular and thromboembolic complications,[149–151 154 168 173 178 183 189] treatment of chronic and end-stage kidney disease,[159 163 202 205] family planning,[199] COVID-19[156 179 186 190 193 194] and patient education.[161] Some of the limited evidence is briefly summarised here:

- Kidney transplantation leads to a 70% reduction in mortality (RR=0.30, 95% CI 0.25 to 0.37) compared with non-transplanted AAV patients with ESKD, resulting from reduced cardiovascular events and death.[159 202]
- CYC treatment is associated with earlier menopause and primary ovarian insufficiency in premenopausal women with AAV.[199]
- The SLR identified one randomised, controlled study in which a 1-day educational programme for patients with AAV showed to increase AAV-specific knowledge compared with the control group.[161]
- Patients with AAV are at higher risk for poor COVID-19 outcomes due to the treatments used, especially due to high-dose GCs, CYC and RTX.[190 193]

Reports on vaccine antibody response are scarce, data point towards an impaired serological response to vaccination after B-cell depleting therapy.[179 186]

In summary, data are limited on several aspects of general management of AAV. A broader spectrum of studies that identify general principles applicable to several inflammatory diseases has to be taken into consideration to improve the management of AAV patients.

DISCUSSION

Key findings of this SLR are summarised in table 4. The prevalence of EGPA is lower compared with that of other AAV syndromes,[217] resulting in fewer clinical trials and in previous EULAR recommendations for the management of AAV,[1] the treatment recommendations for GPA, MPA and EGPA were combined. Major progress was made by the publication of studies including mainly or exclusively EPGA patients.[2–4 37] The resulting data now allow to generate specific treatment recommendations for EGPA.

First, for remission induction in newly onset EGPA without adverse prognostic factors (defined by the 1996 FFS), it has been shown that GC monotherapy induces remission in the majority of patients,[3 27 210] but the addition of AZA to GC has not been demonstrated to improve the rate of initial remission, relapse rates or GC dependency.[3] Second, for patients with adverse prognostic factors (defined by a FFS ≥1), a recent RCT indicates that outcomes with RTX are similar to the conventional strategy using CYC. Third, MEPO has been shown to lead to higher rates of remission and lowers GC doses needed.[2]

For remission maintenance treatment in EGPA, available data are scarce: MTX showed similar remission rates compared with CYC when given as maintenance treatment after CYC induction in EGPA with adverse prognostic factors.[37] AZA, if added in newly onset patients without adverse prognostic factors, showed no reduction of relapse risk of GC doses, whereas MEPO added to standard treatment in relapsing or refractory EGPA, resulted in higher rates of remission and lower GC demand.[2 3]

There are some limitations to the available studies of EGPA: first, due to the rarity of EGPA, some trials have included patients with various vasculitides, in addition to EGPA. The analysis of EGPA subsets in mixed populations, high concomitant GC doses and unblinded trial design introduce risk of bias.[3 37 38] For some aspects of management, there is only retrospective cohorts or case-series available.[19 33] However, it is a tremendous success, that several RCTs informing the management of EGPA were successfully conducted. Second, the 1996 version of the FFS[218] is the scoring system used in several trials to separate EGPA patients with or without adverse prognostic factors to guide their treatment.[3 4 37 38] The primary aim of the FFS is the prediction of mortality. For patients with newly onset EGPA and an FFS of zero, an improvement of outcomes by the addition of AZA or RTX to GC has not been shown in RCTs,[3 4] but at the same time, rates of patients with insufficient response, relapse or GC-dependent disease course are high (>40%) and GC-associated damage in patients treated with GC-monotherapy remains high.[210] This clearly demonstrates an unmet need of successful GC-sparing strategies in EGPA. Disease damage does not only result from long-term GC treatment but also from the preceding disease activity of relapsing EGPA.[32] Even though identifying risk factors of mortality to initiate a potent immunosuppressive treatment is one key factor for choosing a sufficient induction regimen, additional factors addressing relapse risk and predicting GC-dependent disease should be incorporated to guide therapy. Third, GC dependency may also be caused by insufficient asthma control or relapsing sinusitis in EGPA.[3 25] The co-occurrence of asthma and sinonasal manifestations remains a factor that prevents successful tapering of GC and may be difficult to clearly separate from other 'vasculitic' manifestations of EGPA.

For the areas of diagnostic testing and follow-up, there are some recent advances:

Histologic findings in kidney biopsies (sometimes combined with other factors, eg, eGFR) can be used to predict renal outcomes of patients with kidney involvement.[61 77 89 131 138] The results of validating cohort studies (supported by a recent meta-analysis[81]) show superior diagnostic accuracy of antigen-specific immunoassays for PR3-autoantibodies and MPO-autoantibodies compared with ANCA testing via IIF[5 67 145] and, hence, are suitable to be used as primary serologic diagnostic test. These development has recently led to a change in the international recommendations for ANCA testing.[6 219] Diagnostic accuracy studies reporting sensitivity or specificity of ANCA for EGPA were not identified. Even though the course of ANCA levels and (after RTX treatment) B cells shows some predictive value for relapse and remission, they lack the sensitivity and specificity to base treatment decisions solely on them. Overall bias of diagnostic studies on ANCA testing was low.

For several aspects of general management, AAV-specific data are scarce and the adoption of overarching principles applied in various autoimmune conditions seems necessary to guide management in AAV.[220–223] Infections have been identified as a main risk factor of mortality in AAV[224 225] and evidence supports a treatment with infection prophylaxis with TMS, which reduces the risk of pneumocystis pneumonia and other severe infections in patients treated with CYC, RTX or high-dose GC.[162 176 185 201] Of note, most of these studies are retrospective and some of them are not limited to AAV.

A comprehensive literature search based on questions in PICO format developed by clinicians and patient partners is a major strength of our approach. Especially in retrospective analyses, the subgroups and endpoints that were analysed often have different definitions, which makes direct comparisons difficult. Even though, AAV (and especially EGPA) are rare diseases, major progress has been made in the definition of diagnostic procedures

in AAV and treatment trials in EGPA. For some aspects, unmet needs and data gaps remain (table 5).

This SLRs identified recent developments affecting key areas of AAV diagnosis and follow-up and EGPA treatment. Our results provide comprehensive evidence for most aspects of managing AAV to inform the 2022 update of the EULAR recommendations for these diseases.[8]

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